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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,576	07/17/2000	HANS CHRISTIAN THOGERSEN	THOGERSEN=1	1127

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,576	THOGERSEN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,19,22,23 and 68-134 is/are pending in the application.

4a) Of the above claim(s) 92,93,95-97,100,101,104 and 105 is/are withdrawn from consideration.

5)☒ Claim(s) 22,23,68-72,80-91,94,98,99,102,103 and 109-111 is/are allowed.

6)☐ Claim(s) 1,19,73-79,106-108,112-117,119-124 and 126-134 is/are rejected.

7)☒ Claim(s) 118 and 125 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION.

1. Claims 1, 68 and 83 have been amended. Claims 1, 19, 22, 23 and 68-134 are pending. Claims 92, 93, 95-97, 100, 101, 104 and 105, drawn to non-elected inventions, remain withdrawn from consideration. Claims 1, 19, 22, 23, 68-91, 94, 98, 99, 102, 103 and 106-134 are under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. Claims 73-79, 107, 113-117 and 119-123 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) The recitation of "trimeric polypeptide complex" in claim 74 lacks antecedent basis in claim 1.

(B) It is unclear how claim 107 further limits claim 90, because the recitation of "further processing" does not clearly define an additional active method step.

(C)Claims 73, 75-79, 113-117, 119-123 are vague and indefinite for reliance on a Figure in the disclosure. The M.P.E.P (2173.05(s)) states
Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

4. Claims 108 and 127 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Claims 108 and 127, require a "molecule having antibody characteristics. The specification lacks an adequate written description for a "molecule having antibody characteristic" . The specification describes only antibodies and antigen-binding fragments of antibodies, such as Fab fragments and scFv. When given the broadest reasonable interpretation, "a molecule having antibody characteristics" is not confined to antigen-binding antibody fragments, but reads on any molecular structure which binds a desired target. The disclosure of receptor ligands, antibodies and antigen-binding fragments of antibodies fails to describe this genus of molecules because the genus contains molecules which differ significantly in structure from antibodies and receptor ligands and includes small organic molecules which have not been described by the specification. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

A definition by function, such as "a molecule having antibody characteristics" does not suffice to define the genus because it is only an indication of what the molecule does, rather than what it is. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed invention with respect to the broadly claimed "molecule having antibody characteristics".

5. Claims 1, 19, 112, 124, 126, 131, 132 and 134 are rejected under 35 U.S.C. 102(b) as being anticipated by Forsburg et al (Gene, June 3, 1997, Vol..191, pp. 191-195) as evidenced by

Chen et al (Biochemistry, 1998, Vol. 37, pp. 13643-13649) and Kim et al (Biochemistry, 1996, Vol. 35, pp. 5359-5365) and Nautiyal et al (Biochemistry, 1995, Vol. 34, pp. 11645-11651).

It is noted that the specification defines TTSE as including variants of tetranectin trimerizing structural element which have been modified in amino acid sequence without adversely effecting the trimerization properties relative to those of the native tetranectin family (page 14, lines 5-10). Therefore, when given the broadest reasonably interpretation, the recitation of "TTSE" does not imply any specific degree of structural homology to the tetranectin trimerizing element because no limitations have been placed on the number of amino acid substitutions that can be effected without altering the trimerizing properties of the molecules.

Claim 1 is drawn to a monomer polypeptide construct comprising at least one tetranectin trimerizing structural element(TTSE) which is covalently linked to at least one heterologous moiety, wherein said TTSE is capable of forming a stable triple alpha helical coiled coil complex with two other TTSEs, wherein said complex remains a trimer at a temperature of at least 60 degrees, and wherein the heterologous moiety is different from any of the fusion proteins CIIH6FXTN123, H6FXTN123, H6FXTN12, H6FCTN123 (SEQ ID NO:24-27). Claim 19 is drawn to an oligomer comprising at least two monomer polypeptide constructs according to claim 1. Claim 112 is drawn to an oligomer construct comprising three monomers polypeptide constructs according to claim 1. Claim 123 embodies the monomer polypeptide construct of claim 1 wherein the TTSE comprising a repeated heptad having the formula a-b-c-d-e-f-g, wherein a majority of the "a" and "d" amino acid residues are hydrophobic. Claim 126 embodies the monomer polypeptide construct of claim 1, wherein the at least one heterologous moiety is selected from the group consisting of a ligand binding structure, a toxin, a detectable moiety, and in situ activatable substance, an enzyme, a radioactive moiety, a cytokine, a non-proteinaceous polymer, a photocross-linking agent and a group facilitating conjugation of the polypeptide to a target wherein the conjugation encompasses both covalent and non-covalent linkages. Claims 131 and 132 embody the monomer polypeptide construct of claim 126 wherein at least one heterologous moiety is positioned C-terminally or N-terminally, respectively. Claim 134 embodies the monomer polypeptide construct of claim 126 wherein the heterologous moiety is covalently linked to the monomer polypeptide via a peptide bond to a N terminus of the

monomer polypeptide, a C-terminus of the monomer polypeptide, a side chain of the monomer polypeptide via a bond to a cysteine residue, or a combination of these locations.

Forsburg et al disclose C-terminally HA tagged Cdc19p and N-terminally tagged Cdc19p (page 192, column 2, lines 14-31), which fulfills the specific embodiments of claims 131, 132 and 134 regarding the modifications of the amino anc carboxyl termini. Forsburg et al use the influenza HA as a detectable protein tag (page 191, column 1, lines 4-10). Kim et al provides evidence that influenza HA is a homotrimer consisting of two subunits, HA1 and HA2 which comprises an alpha helix and assembles into a three stranded coil-coil (page 5359, column 1 line 14 to column 2, line 5). Thus, the expressed HA-Cdc19p and Cdc19p-HA product would form an alpha helical coiled-coil trimer. Nautiyal et al provides evidence that coiled-coil sequences comprise a heptad repeat a-b-c-d-e-f-g, in which the "a" and "d" d positions are occupied by hydrophobic amino acids, thus, the influenza HA heptad meets the specific embodiments of claim 123. Chen provides evidence that the trimeric HA fusion protein remains a trimer until 80.5 degrees C, thus meeting the limitation of claim 1 requiring that the complex remains trimeric up to at least 60/ degree C.

6. Claims 1, 19, 106, 112, 124, 126, 127, 129, 131-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pack et al (WO 96/37621, reference AC of the IDS submitted April 23, 2001) in view of Nautiyal et al (Biochemistry, 1995, Vol. 34, pp. 11645-11651).

The specific embodiments of claims 1, 19, 112, 124, 126, 131, 132 and 134 are set forth above. Claim 106 embodies the monomer polypeptide construct of claim 1 wherein the at least one heterologous moiety does not exclusively facilitate expression and/or purification of the monomer polypeptide constructs. Claim 127 embodies the monomer polypeptide of claim 126 wherein the ligand binding structure is a receptor, a ligand binding portion of a receptor, an antibody, an antigen-biding portion of an antibody, a monovalent scFv antibody fragment and a Fab antibody fragment. Claim 129 embodies the monomer polypeptide of claim 126 wherein the detectable label is selected from the group consisting of a fluorescent label, a radioactive label and an enzymatic label. Claim 133 embodies the monomer polypeptide of claim 126 which comprises at least one heterologous molecule positioned N-terminally to the monomer

polypeptide and at least one heterologous molecule which is pointed C-terminally to the heterologous polypeptide.

Pack et al teach peptidic multimerization devices providing for the targeted multimerization of enzymes, toxins, cytokines, kinases, phosphatases, lectins, peptidic hormones, cell adhesion proteins, metal binding domains, peptidic vaccines, bioactive peptides or soluble cell-surface proteins (page 22, last paragraph). Pack et al teach that the multimeric proteins of the invention can be encoded and translated a single, contiguous polypeptide chain comprising the general structure of domain1-linker1-multimerization device-linker2-domain2 with posttranslational self-assembly (page 10, second full paragraph). Pack et al teach small peptidic multimerization devices which at least form trimers or higher-order oligomers (page 16, lines 1-7 and 17-20, under "Detailed Description"). Pack et al also teach multimeric proteins comprising scFv fragments, as in the general structure scFv1-linker1-multimerization device-linker2-scFv2 (page 12, lines 24-27). Pack et al do not specifically teach multimerization devices which are capable of forming an alpha helical coiled coil trimer which remains a trimer up to at least 60 degrees C.

Nautiyal et al teach a heterotrimeric coiled coil comprising a hetpad repeat wherein positions "a' and "d" are occupied by hydrophobic amino acid sequences (page 11645, second column, lines 9-19) and three monomer polypeptides which were designed to form the coiled coil (page 11646, second column, lines 23-27 under the heading "Experimental Procedures"). Nautiyal et al teach that a mixture comprising equimolar concentrations of each peptide was fully helical (page 11648, first column, lines 11-14) and remained trimeric until 87.5 degrees C (page 11648-11649, bridging sentence) thus fulfilling the specific embodiments of claim 1 regarding temperature stability at 60 degrees C. Nautiyal et al teach that the ability and specificity of the heterotrimeric ABC peptides can be used as an autonomous oligomerization domain for mediating the association of three different proteins (last paragraph).

It would have been prima facie obvious at the time the claimed invention was made to use the ABC peptides as an autonomous oligomerization domain in the peptidic multimerization devices taught by Pack et al. One of skill in the art would be motivated to do so by the teachings of Pack et al on the requirement that the small, peptidic multimerization devices which at least

form trimers. One of skill in the art would recognize that the heteroligomers of Nautiyal et al would function as the multimerization device in the method of Pack et al.

7. Claims 1, 19, 106, 112, 124, 126, 127, 129-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pack et al (WO 96/37621) and Nautiyal et al (Biochemistry, 1995, Vol. 34, pp. 11645-11651) as applied to claims 1, 19, 106, 112, 124, 126, 127, 129, 131-134 above, and in further view of Hoppe et al (WO 95/31540, cited in a previous action).

Claim 130 embodies the monomer polypeptide construct of claim 126, wherein the non-proteinaceous polymer is selected from a polymeric alkaloid, a polyalcohol, a polysaccharide, a lipid and a polyamine.

Hoppe et al teach monomer polypeptide constructs comprising collectins which form trimeric alpha helices. Having a lower melting temperature than that claimed. Hoppe et al teach that the monomer polypeptide constructs may comprise heterologous moieties such as (viii) carbohydrates, (ix) lipid-containing structures and (x)DNA or RNA derivatives, which fulfill the specific embodiments of claim 130.

It would have been prima facie obvious at the time the claimed invention was made to use the heterologous moieties taught by Hoppe et al in the monomer polypeptides rendered obvious by the combination of Pack et al and Nautiyal et al. One of skill in the art would have been motivated to do so because both of Pack et al and Hoppe et al disclose the delivery of heterologous molecules by means of a multimerization unit.

8. Claims 1, 19, 106, 112, 124, 126-129 and 131-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pack et al (WO 96/37621) and Nautiyal et al (Biochemistry, 1995, Vol. 34, pp. 11645-11651) as applied to claims 1, 19, 106, 112, 124, 126, 127, 129, 131-134 above, and in further view of Schlom (In: The Molecular Basis of Clinical Oncology, 1991, pp. 95-144.).

Claim 128 embodies the monomer polypeptide of claim 126 wherein the toxin is ricin.

The combination of Pack et al and Nautiyal et al render obvious the instant invention wherein the monomer construct is scFv1-linker1-trimerization unti-linker2-scFv2 for the reasons se forth above. Pack et al also teaches that the heterologous moieties can be toxins (page

22, last paragraph). Nautiyal et al specifically teach that the ability and specificity of the heterotrimeric ABC peptides can be used as an autonomous oligomerization domain for mediating the association of three different proteins (last paragraph).

Schlom teaches that monoclonal antibodies can be used to deliver the toxin ricin to cancer cells (pages 107-108, under the heading "Drug and Toxin mAb Conjugates"). Schlom also teaches the used of scFv for targeting cancer cells in vivo (pages 119-123, under the heading "Single Chain Antigen Binding Proteins").

It would have been prima facie obvious at the time the claimed invention was made to include in the heterotrimer rendered obvious by the combination of Pack et al and Nautiyal et al, a monomer peptide of ABS conjugated or fused to ricin, and a monomer peptide comprising the scFv1-linker1-trimerization unti-linker2-scFv2 domains. One of skill in the art would have been motivated to do so by the teachings of Nautiyal et al on the ability of the ABS trimer to associate three different proteins, and the teachings of Schlom on the targeting of cancer cells by scFv and the killing of cancer cells by the administration of ricin conjugated to monoclonal antibodies. One of skill in the art would have been motivated to administer to an individual in need thereof a construct containing tumor targeting scFv and the toxic moiety of ricin in order to kill tumor cells.

9. Claims 118 and 125 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. All other rejections and objections as set forth in the previous Office action are withdrawn.

11. Claims 22, 23, 68-72, 80-91, 94, 98, 99, 102, 103, 109-111 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
5/2/2005

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